

78.(NEW) A method for increasing the sensitivity of an assay comprising carrying out a bioluminescent reaction in the presence of an organic compound that reduces autoluminescence by at least about 10 fold, and that reduces luminescence that is dependent on the presence of a bioluminescent enzyme by less than about 7 fold.

REMARKS

Claims 1-75 were pending; claims 58-75 were subjected to a restriction requirement and withdrawn from consideration by the Examiner; and claims 76-78 have been added. Accordingly, claims 1-78 are pending.

Applicant would like to thank Examiner Mahreen Chaudhry and Primary Examiner Ralph Gitomer for the courtesy extended during the telephonic interview on 21 May 2002. The below signed attorney, inventor Dr. Keith Wood, and assignee's patent liaison Rosemarie Kirwin called the above Examiners to discuss the outstanding rejections under 35 U.S.C. §112, second paragraph, and 35 U.S.C. §103(a).

During the phone interview, Applicant's attorney pointed out that the pending claims (as well as the new claims 76-78 that were proposed during the interview) are directed to methods for improving the sensitivity of bioluminescent assays; that bioluminescent assays differ significantly from other types of luminescent assays, such as peroxidase assays; and as a result, that the pending claims are not *prima facie* obvious over the disclosure of Mitoma or Kricka.

Additionally, the Examiner, maintained her position that the claims are indefinite and fail to meet the requirements of 35 U.S.C. §112, second paragraph. Agreement was not reached on this point during the interview.

The above account is believed to be a complete and accurate summary of the telephonic interview as required by 37 C.F.R. §1.133. If the Examiner believes that this summary is inaccurate or incomplete, Applicant respectfully requests that the Examiner point out any deficiencies in her next communication so that Applicant can amend or supplement the interview summary.

Claims 58-75 were subjected to a restriction requirement and withdrawn from consideration by the Examiner. This restriction requirement is respectfully traversed.

If the search and examination of an entire application can be made without serious burden, the Examiner must examine it on the merits, even though it includes claims to distinct and independent inventions. M.P.E.P. §803. It is respectfully submitted that the compounds recited in claims 58-75 are all “organic compounds.” Thus, both the search and the examination of claims 1-57, would necessarily encompass the subject matter of claims 58-75. Accordingly, it is respectfully submitted that the search and examination of claims 58-75 would not place an additional burden on the Examiner. As a result, the restriction requirement is improper.

Additionally, in order to establish that combination and sub-combination inventions are distinct, two-way distinctness must be demonstrated; the burden is on the Examiner to suggest an example of separate utility. M.P.E.P. §806.05(c). In the Final Office Action, the Examiner stated “The sub-combination has separate utility in other combinations.” It is respectfully submitted that the Examiner’s statement is not sufficient to meet the Examiner’s burden. There is no utility identified in this statement. Applicant requests that the Examiner identify what “other combinations” are intended, and what such “other combinations” would be useful for. Without this information, the restriction requirement is improper and should be withdrawn.

Finally, if the Examiner maintains the restriction requirement, and the elected claims (1-57) are found to be patentable, Applicant requests that the restriction requirement be withdrawn, that claims 58-75 be rejoined, examined, and found allowable. M.P.E.P. §809.

Claims 1-34 were rejected under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

35 USC § 112, Second paragraph, requires that the claims particularly point out and distinctly claim the subject matter which the applicant regards as his invention. The instant claims recite “an organic compound” that has certain specifically recited properties. For example, in claim 1, the organic compound is present in a bioluminescent assay, and the organic compound “reduces luminescence that is not dependent on the presence of an analyte by at least

about 10 fold, and [that] reduces luminescence that is dependent on the presence of an analyte by less than about 7 fold.”

As discussed in the previous response, the term “organic compound” is defined in the specification at page 10, line 11, as a compound that “comprises one or more carbon atoms.” It is submitted that this definition is consistent with the established usage of the term in the art. Therefore, the term “organic compound” is not indefinite. Additionally, the specification contains numerous working examples (see pages 18-34) which demonstrate how one skilled in the art can identify an organic compound that possesses the specific properties recited in the claims. Thus, one skilled in the art can readily identify, without undue experimentation, if a compound is an “organic compound” and can also readily determine if the organic compound has the recited properties, e.g. reduces luminescence that is not dependent on the presence of an analyte by at least about 10 fold, and reduces luminescence that is dependent on the presence of an analyte by less than about 7 fold as recited in claim 1, which is directed to a method for increasing the sensitivity of a bioluminescent assay. Accordingly, the instant claims “particularly point out and distinctly claim the subject matter which the applicant regards as his invention.”

In the Office Action, the Examiner states that “the term “organic compound” is broad and encompasses more than the specification could possibly support (page 3)” and that “the term “organic compound” is unduly broad especially in view of the examples of suitable organic compounds provided in the specification (page 4).” It is submitted that, even if these statements were correct, they would only be relevant to a rejection under 35 USC § 112, first paragraph. *In re Swinehart* 169 U.S.P.Q. 226, 229 (copy enclosed). However, such a rejection has not been made. Additionally, in the above referenced phone interview, the Examiner confirmed that the rejection had only been made under the second paragraph of 35 USC § 112. Accordingly, the Examiner’s remarks do not support the rejection under 35 USC § 112, second paragraph.

At page 4 of the Office Action, the Examiner also states that the term “organic compound” does not adequately define a specific chemical compound or specific class of compounds appropriate for utilization in the recited methods and kits. The claims define such chemical compounds functionally without recitation of a specific chemical structure beyond the fact that such compounds are organic.” The second paragraph of 35 USC § 112 does not prohibit

the use of a functional description for a claim element. Accordingly, the Examiner has applied an inappropriate legal standard to establish the rejection under 35 USC § 112, second paragraph. Denial of a patent is not required solely because of the type of language used to define the subject matter for which patent protection is sought. *In re Miller* 169 U.S.P.Q 597, 599 (copy enclosed). There is nothing intrinsically wrong in using functional language, defining something by what it does rather than by what it is, in drafting patent claims; courts have even recognized the practical necessity for the use of functional language. *In re Swinehart* 169 U.S.P.Q. 226, 228.

The second paragraph of 35 USC § 112 only requires that the claims particularly point out and distinctly claim the subject matter which the applicant regards as his invention. As discussed above, one skilled in the art can readily identify if a compound is an "organic compound" and can also readily determine if the organic compound has the specific properties recited in the claims. Thus, the claims meet the requirements of 35 USC § 112, second paragraph. In light of the above remarks, withdrawal of the rejection under 35 USC § 112, second paragraph is respectfully requested.

Claims 1-3, 8-12, 16-21 and 35-53 were rejected under 35 USC § 103(a) as being unpatentable over JP 07067696A published by Mitoma et al, and claims 1-3, 8-31 and 34-57 were rejected were rejected under 35 USC § 103(a) as being unpatentable over U.S. Patent No. 5,629,168 issued to Kricka. These rejections are respectfully traversed.

As discussed in the previous response, Mitoma discusses a method of reducing background luminescence in a mixture where luminescence is generated by the treatment of a 2,3,-dihydro-1,4-phthalazinedione with heme or peroxidase, in the presence of an oxidizing agent. Kricka discusses a method for increasing the light output and/or the signal-to-background ratio of light output from a chemiluminescent reaction of dihydrophthalazinedione, a peroxidase enzyme catalyst and an oxidant, by carrying out the reaction in the presence of an enhancer which is an aromatic organo-boron compound.

Applicant discovered that it is possible to increase the sensitivity of an assay that utilizes a bioluminescent enzyme by selectively reducing unwanted luminescence from non-bioluminescent sources, without similarly reducing signal. This result was unexpected and was undisclosed in the art. The instant claims are directed to Applicant's invention.

As discussed during the above referenced telephone interview, there are several distinct classes of luminescent reactions. One specific class of luminescent reactions utilizes bioluminescent enzymes, which have unique properties not found in other classes of enzymes associated with luminescent reactions. In particular, bioluminescent enzymes have evolved specifically for the purpose of generating light (see the specification at page 8, lines 11-17). Applicant believes the structure of bioluminescent enzymes allows them to minimize luminescence quenching by excluding water (and other quenching molecules) from the excited-state intermediate while light is being produced. This is not true of the peroxidases reported in Mitoma and Kricka. Additionally, bioluminescent enzymes catalyze monooxygenation using molecular oxygen, in contrast to the peroxidases reported in Mitoma and Kricka, which catalyze single electron transfers using hydrogenperoxide. Accordingly, the mechanism by which bioluminescent reactions generate light differs considerably from the mechanism by which the peroxidases reported in Mitoma and Kricka generate light.

Claims 1 and 3 recite a “bioluminescent assay;” claims 76 and 78 recite a “bioluminescent reaction;” and claim 77 recites a “bioluminescent enzyme.” These claims all relate to methods that involve bioluminescent enzyme systems that differ significantly from the peroxidase enzymes reported in Mitoma and Kricka.. Claim 2 recites “a luminogenic molecule bound to an enzyme.” In the peroxidase system reported in Mitoma and Kricka, there are no “luminogenic molecules bound to enzymes.” Thus, the method of claim 2 also differs significantly from the disclosure of Mitoma and Kricka.

The Examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves, or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. M.P.E.P. §2142.

The Examiner has not identified any motivation for one skilled in the art to modify the peroxidase systems reported in Mitoma or Kricka in the manner necessary to arrive at the

instantly claimed methods.

Additionally, in light of the considerable differences between the peroxidase systems discussed in Mitoma and Kricka and the assay systems recited in the instant claims, it is submitted that Mitoma and Kricka would not have provided one skilled in the art with a reasonable expectation that the instantly claimed methods for improving assay sensitivity could have been successfully carried out.

Finally, the instant claims recite specific selective quenching effects. Mitoma and Kricka are silent on these recited effects. Accordingly, Mitoma and Kricka do not suggest all the elements of the instant claims.

In light of the above remarks, it is respectfully submitted that the Examiner has not met any of the three criteria required to establish a *prima facie* case of obviousness over Mitoma or Kricka.

The Examiner stated that “it would have been obvious to one having ordinary skill in the art to have reduced background luminescence from any source using an organic compound as taught by Mitoma et al. since Mitoma et al. teach a general method of reducing background luminescence with specific organic compounds. (Office Action at page 5)” It is respectfully submitted that the Examiner’s conclusion is incorrect. As discussed above, there are several significant differences between the luminescent system reported in Mitoma and the enzyme systems recited in the instant claims. In light of these differences, it would not have been obvious to one having ordinary skill in the art to use the compounds discussed in Mitoma to reduced background luminescence in an enzyme system recited in the instant claims. In fact, one skilled in the art would have had no expectation that the compounds discussed in Mitoma could be used in a method to selectively reduce background luminescence as claimed.

At page 6 of the Office Action, the Examiner draws a similar conclusion regarding the disclosure of Kricka: “it would have been obvious to one having ordinary skill in the art to have utilized the method taught by Kricka for reducing background luminescence from any source and thus increase luminescent assay sensitivity... (Office Action at page 6-7).” In light of the significant differences between the luminescent system reported in Kricka and the enzyme systems recited in the instant claims, it would not have been obvious to one having ordinary skill

in the art to use the methods of Kricka to reduced background luminescence in an enzyme system of the instant claims. In fact, one skilled in the art would have had no expectation that the compounds discussed in Kricka could be used in a method to selectively reduce background luminescence as claimed.

In light of the above remarks, Applicant respectfully requests the Examiner to withdraw the rejections under 35 U.S.C. § 103(a) over Mitoma and over Kricka.

Claims 1-34 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Wood (U.S. Patent No. 5,814,471). This rejection is respectfully traversed.

Wood '417 discloses a method for improving the kinetics of light production from luciferase activity (i.e. a rapid increase in intensity followed by a rapid decrease in the first few seconds, followed by a further decay that may last hours).

As discussed in the previous response, Wood does not suggest that unwanted luminescence can be reduced in any way. Accordingly, Wood provides no motivation to reduce unwanted luminescence as recited in the instant claims. Additionally, Wood would not have provide one skilled in the art with a reasonable belief that unwanted luminescence could have been selectively reduced using the method reported therein. Thus, the instant claims are not *prima facie* obvious over the disclosure of Wood.

At pages 8-9 of the Office Action, the Examiner states that "Wood et al. is directed to the inclusion of organic compounds in a bioluminescent reaction for the purpose of improving the kinetic of luminescence produced by a luciferin reaction. The claims recite 'a method for increasing the sensitivity of a bioluminescent assay comprising carrying out the assay in the presence of an organic compound...' The method disclosed by Wood et al. would be encompassed by such method." The Examiner has failed to account for (and omitted from the above passage from the Office Action) an entire portion of the instant claims. The instant claims recite a selective reduction of unwanted luminescence. As stated before, the method reported by Wood solves a completely different problem (improving the kinetics of light production). Wood does not suggest that any reduction of unwanted luminescence can be achieved. Thus, the instantly claimed methods and kits are not *prima facie* obvious over the disclosure of Wood.

At page 9 of the Office Action, the Examiner states "Since applicant does not provide any

structural characteristics of the recited organic compound and merely discloses its functional characteristics, the method taught by Wood et al., of including a thiol containing compound in a luciferase reaction in order to improve luminescence characteristics would obviate the method as claimed.” Again, the claims recite a selective reduction of unwanted luminescence. This is an element of the claims. All words in a claim must be considered in judging the patentability of that claim against the prior art. *In re Miller* 169 U.S.P.Q 597, 600. Therefore, the functional language in the instant claims cannot be ignored by the Examiner.

A reference must teach or suggest all of the claim limitations to establish a *prima facie* case of obviousness. M.P.E.P. §2142. Since Wood does not suggest that any reduction of unwanted luminescence can be achieved, the instant claims are not *prima facie* obvious over the disclosure of Wood. Accordingly, the Examiner is requested to withdraw the rejections under 35 U.S.C. § 103(a) over the disclosure of Wood.

As a final note, claims 76-78 have been added. These claims were discussed with the Examiners during the above referenced telephone interview. If the Examiner maintains any of the above rejections, Applicant requests that the Examiner consider whether the prosecution of claims 76-78 would remove any of the outstanding rejections prior to appeal. Applicant would consider amending claims 1-3 to mirror claims 76-78 if such an amendment would eliminate any of the existing rejections.

AMENDMENT AND RESPONSE UNDER 37 CFR § 1.116 - EXPEDITED PROCEDURE

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Applicant respectfully submits that the claims (1-78) are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney 612-359-3265 to facilitate prosecution of this application.


If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

ERIKA HAWKINS ET AL.

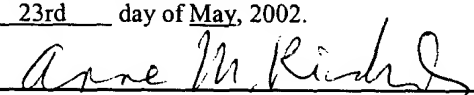
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